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conced.

deliverable upon the occurrence of a triggering condition comprising a change in pH or ionic strength, wherein said lipid vesicle structure substantially comprises an [amino] acyl N<sub>n</sub>,N<sub>n</sub>-dimethyl-1-[d<sub>n</sub>]-diamino alkyl chain salt banded to a fatty acid (A-ADDA) such that a hydrophillic portion of said vesicle is cationic, whereby the resulting vesicle is substantive to hair, tissue culture cells, epithelial cells and skin to enhance the system's ability to deliver said material.

[ In claim 37, last line, after "hair" insert --, tissue culture cells, epithelial cells--.

B<sup>3</sup>

25 38. (Amended) The system defined by claim <sup>21</sup>38, wherein the material [may be chosen] is selected from the group consisting of [:] hydrophobic and hydrophillic materials.

#### REMARKS

Further to the Examiner's Final Office Action mailed May 18, 1998 applicants filed a Continuing Prosecution Application on July 20, 1998 with appropriate extension fees. In a telephone call with the Examiner on July 17, 1998, applicants informed the Examiner that a Preliminary Amendment would be filed on July 29, 1998. In a subsequent telephone call on July 29, 1998, the Examiner Indicated that he would not issue any action until receiving said Preliminary Amendment and that the Amendment, filed today, would be entered. Applicants wish to thank the Examiner for his time during these calls.

For the convenience of the Examiner, applicants have supplied a copy of the current claims of the application. (See attached Exhibit A.) These claims incorporate the amendments submitted with the October 27, 1997 amendment as well as the amendments submitted with this amendment. Amendments submitted herewith are indicated by underlining and bracketing where appropriate.

Claims 9 and 26 have been canceled herein, without prejudice.

Although the Office Action indicates that claims 1-10, 18-26 and 33-38 were pending, actually claim 17 and 39 were pending as well. Claims 9 and 26 have been canceled. Therefore, claims 1-8, 10, 17-25 and 33-39 are pending and are at issue.

Claims 1, 18, 35 and 37 have been amended to further clarify the characteristics of the resulting vesicle. Support for the addition of tissue culture cells and epithelial cells is found in the specification in Example 4 at page 16, line 19. Claims 1, 18 and 35 have also been amended to correct an obvious editorial error in the chemical structure of the A-ADDA molecule. Claims 4-7, 17 and 21-24 have been amended to delete the phrase "includes" and insert the phrase "comprises". Claim 8 has been amended to depend from claim 7. Claim 10 has been amended to delete the phrase "further including" and insert the phrase "wherein the"; to delete the phrase "which includes" and insert the phrase "comprises"; and to delete the phrase "around" as suggested by the Examiner. Claim 33 has been amended to change the dependency from canceled claim 27 to

claim 18 and to change the phrase "including" to "comprising". Claim 34 has also been amended to change the dependency from canceled claim 27 to claim 18 and to change the phrase "Includes" to "comprises".

Claim 35 has also been amended to add specific triggering conditions, namely, a change in pH or ionic strength. Support for this amendment is found in the specification at page 4, lines 12-14; page 6, lines 9-11; page 8, line 17; page 9, lines 1-9; page 15, lines 4-13; and page 16, lines 6-10. Claim 39 has been amended to properly claim the Markush group.

The Examiner is requested to enter these amendments as they are directly responsive to the present rejections or are made in order to more particularly claim and further clarify the invention and will not require any further search.

Claims 10, 18-26 and 33-38 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner questions whether CATEZOMES are liposomes made of instant lipids and whether they are available commercially.

The rejection is respectfully traversed, and reconsideration is requested. The specification clearly describes the liposomes of the invention and states that "[s]uch liposomes are marketed under the tradename CATEZOMES™." (See specification at page 6, lines 11-14.) Thus, the disclosed Catezomes are clearly the liposomes of the invention. The present specification supports the use of this term.

In addition, applicants enclose herewith a copy of a Declaration under 37 C.F.R. 1.132 executed by inventor David Watkins, Ph.D. which was facsimile filed with the Examiner on February 17, 1998. (Attached as Exhibit B.) In this declaration, Dr. Watkins states that he is "an Inventor of this invention, which includes apparatus and process for preparing cationic liposomes (or CATEZOMES™)," that he is the author of a 1997 article entitled "Catezomes™: a novel delivery system for hair conditioning" and that the "cationic liposomes disclosed by this invention were not on sale, nor commercially used before January 10, 1996." (See Declaration at paragraphs 10, 11 and 13.) This date is less than one year before the filing date of the application, namely January 31, 1996.

Therefore, the rejection should be withdrawn.

The Examiner has rejected claims 33-38 under 35 U.S.C. § 112, second paragraph for indefiniteness. However, applicants note that the Examiner has pointed to a number of additional claims in his comments.

The rejection is respectfully traversed, and reconsideration is requested. The Examiner has rejected claims 33-38 as being indefinite "since they depend from canceled claim 27". Claims 33 and 34 have been amended to depend from claim 18. Applicants note that claims 35-38 do not depend from any canceled claim.

The Examiner states that it is unclear what is meant by "fatty acid (A-ADDA)" in claim 35. A-ADDA is an acronym for the acyl  $N_n$ ,  $N_n$ -dimethyl-1,n-

diamino alkyl chain salt bonded to a fatty acid which is recited in the claim. The specification explains that the acyl  $N_n,N_n$ -dimethyl-1,n-diamino alkyl chain is defined as ADDA (see specification at page 6, line 20) and that an additional fatty acid is salt bonded through its carboxyl group at the quaternary amine group of the ADDA to produce an acyl ADDA or "A-ADDA" salt (see specification at page 6, lines 23-25).

In light of the foregoing, applicants submit that the rejection of claims 33-38 under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Examiner's additional comments regarding the claims are summarized and addressed as follows:

The Examiner states that the term "includes" in claims 4-7, 9, 16, 17, 21-23, 26-27 and 33-35 is indefinite. Claims 16, 17 and 27 were canceled in the previous October 27, 1997 amendment. Claims 9 and 26 are canceled herein. (See discussion below.) Applicants have amended claims 4-7, 21-23 and 33-35 to delete the phrase "includes" and insert "comprises".

The Examiner also states that it is unclear what is intended by the phrase "said buffer....dispersing includes  $H_2O$ " in claims 4 and 21. The claim now recites a buffer which comprises water.

The Examiner states that claims 9 and 26 are indefinite. Claims 9 and 26 have been canceled.

The Examiner states that claim 10 should recite adequately how A-

ADDA is prepared and suggests deleting the phrase "around" in claims 10, 11, 27 and 28 and the phrase "about" in claims 11, 14 and 31. Claims 11, 14, 27, 28 and 31 were canceled in the previous October 27, 1997 amendment. Claim 10 has been amended to delete the phrase "around". Support for this amendment is found in the specification at page 10, line 3.

The Examiner questions the phrase "occurrence of a triggering condition" in claim 35. Claim 35 has been amended to define such conditions as a change in pH or ionic strength. Support for this amendment can be found in the specification at page 4, lines 12-14; page 6, lines 9-11; page 8, line 17; page 9, lines 1-9; page 15, lines 4-13; and page 16, lines 6-10. As stated in the specification, the liposome vesicles of the invention provide for liposomes which, upon interaction at the delivery site, release encapsulated material due to a triggering condition or instability related to pH and/or ionic strength.

The Examiner states that "[I]t is unclear where the proteins are and how they readily adhere as recited in claim 36." Claim 36 depends from claim 35 which recites a lipid vesicle such that a hydrophilic portion of said vesicle is cationic. The specification discloses that, when the liposomes of the invention display a cationic nature at the hydrophilic portion of the molecule, such liposomes possess powerful and useful binding abilities to proteins, such that the liposome vesicles adhere or bind to protein or like molecules. (See specification at page 5, lines 4-5; and at page 7, lines 15-17.) Thus, the protein binding occurs through

Interaction at the cationic hydrophilic portions of the vesicles. Non-limiting examples of protein to which the cationic vesicles adhere can be found in hair shafts, chitin shells of nuts, tissue culture cells, and airway epithelial cells. (See Example 3, page 16, line 5 and Example 4, page 16, line 18.)

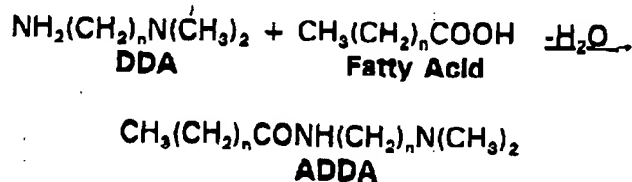
The Examiner states that "[i]t is unclear what 'controlling the salt bridge' in claim 37 means." This claim was previously amended to read as "controlling the stability of a salt bridge linking said fatty acyl and amide." (See October 27, 1997 Amendment.) The specification explains that the stability of the salt bridge between the carboxyl group of the acyl fatty acid and the quaternary ammonium of the ADDA molecule, and thus the stability of the vesicles themselves, can be controlled. (See specification at page 9, lines 5-8; page 14, lines 31-33; and page 15, lines 8-9.)

The Examiner has rejected claims 18-26 and 33-38 under 35 U.S.C. §102(b) as anticipated by applicants' statement of prior art or EP O 158 441. (See Office Action at page 4.) The Examiner states that "Applicants have not clearly placed on record, when the product CATEZOMES were available to the public." The Examiner also states that EP O 158 441 ("EP '441") "teaches liposomal composition containing instant lipid."

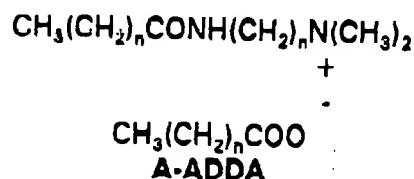
The rejection is respectfully traversed, and reconsideration is requested. The Examiner's attention is respectfully directed to the enclosed Declaration under 37 C.F.R. §1.132 (Exhibit B) and the discussion above which

demonstrate that CATEZOMES™ are the liposomes of the invention and that they were not publicly available more than one year prior to the filing of the U.S. application. The time at which the CATEZOMES™ of the invention were available to the public is clearly on record.

Regarding EP '441, none of the compounds described therein are presently claimed. The liposome vesicles of the present invention are comprised of alkylammonium fatty acid salts. These salts are made as described in the specification at page 6, lines 15-25 and in the examples. A fatty acid is linked via an amide bond to the primary amino group of an N<sub>n</sub>,N<sub>n</sub>-dimethyl-1,n-diamino alkyl chain (DDA) to form an acyl N<sub>n</sub>,N<sub>n</sub>-dimethyl-1,n-diamino alkyl chain (ADDA). This reaction is illustrated as follows:



The ADDA is then mixed with another fatty acid at a pH of around 5 to 11 such that a salt bond is formed between the quaternary amine group on the ADDA and the carboxyl group of the fatty acid. This reaction is illustrated as follows:



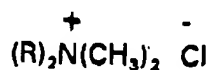
EP '441 does not disclose, nor even suggest, liposome vesicles



comprised of A-ADDA. The Examiner points to the abstract and Examples of EP '441. However, neither the abstract nor the examples disclose the claimed liposomes.

EP '441 discloses phospholipids, glycolipids, and long chain dialkyl dimethyl ammonium compounds for use in generating liposomes. (See EP '441 at page 5, lines 23-26 and page 6, lines 1-6.) None of the phospholipids, glycolipids or long chain dialkyl dimethyl ammonium compounds of EP '441 are the A-ADDA molecules claimed herein. Examples 1-16, 18 and 19 solely disclose the use of lecithin (a phospholipid) while Example 17 discloses the use of phosphatidyl choline (also a phospholipid).

The long chain dialkyl dimethyl ammonium compounds disclosed in EP '441 are distearyl dimethyl ammonium chloride or ditallow dimethyl ammonium chloride. These have the following basic structure:



wherein R is alkyl, namely stearyl or tallow. The long chain dialkyl dimethyl ammonium compounds of EP '441 are clearly not the A-ADDA compounds as claimed.

Therefore the rejection of claims 18-26 and 33-38 under 35 U.S.C. §102(b) should be withdrawn.

Page 12

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Exhibit A

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